PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 04 July 2001 (04.07.01)	
International application No. PCT/US00/18986	**Applicant's or agent's file reference** 15280-397-IPC
International filing date (day/month/year) 12 July 2000 (12.07.00)	**Priority date** (day/month/year) 15 July 1999 (15.07.99)
Applicant ROBERTS, David, D. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

10 January 2001 (10.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer H. Zhou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

10/030735

PATENT COOPERATION TREATY

PCT

REC'D 17 SEP 2001
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
15280-397-IPC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/18986	12/07/2000	15/07/1999
International Patent Classification (IPC) or national classification and IPC C07K7/00		
Applicant THE GOVERNMENT OF THE UNITED STATES....et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/01/2001	13.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Lopez Garcia, F Telephone No. +49 89 2399 2171

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/18986

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-57 as originally filed

Claims, No.:

1-45 as originally filed

Drawings, sheets:

1/20-20/20 as originally filed

Sequence listing part of the description, pages:

1-14, filed with the letter of 29.09.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-45.

because:

   ☒ the said international application, or the said claims Nos. 20-45 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-45 (insofar they have not been searched).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3,5,10,12,16,18,19,23,29-45
	No:	Claims	1,2,4,6-9,11,13-15, 17, 20-22, 24-28
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-45
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	20-45

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I
Basis of the report

1. A partial search has been carried out (see PCT/ISA/210 of 06.02.01). The International Preliminary Examination cannot be carried out for the subject-matter not covered by the Search Report (see Rule 66.1(e) PCT). Thus, examination will be carried for those peptides of claim 1 and/or 8 able to modulate binding of alpha3beta1 integrins with their ligands.

2. A partial search has been carried out (see PCT/ISA/210 of 06.02.01) for claims 20-45. Therefore, examination will be based on the searched matter, ie based on the alleged effects of the compounds /compositions.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 20-45 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

   For the assessment of the present claims 20-45 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2. No opinion will be given for the subject-matter for which an ISR has not been issued (see points I.1 and I.2, above).

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step

or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1: MILES ET AL J. BIOL. CHEM., 1994, vol. 269, p. 30939-30945.
   D2: US-A-5 696 229
   D3: WO 90 03983 A
   D4: WO 98 42737 A
   D5: LI ET AL BIOCHEMISTRY, 1997, vol. 36, p. 15404-15410.
   D6: MOTOYSOHI ET AL J. BIOL. CHEM., 1997, vol. 272, p. 32198-32205.
   D7: SUBRAMANIAM ET AL J. BIOL. CHEM., 1999, vol. 274, p. 11408-11416.
   D8: KRUTZSCH ET AL J. BIOL. CHEM., vol. 274, 1999, p. 24080-24086.
   D9: FAISAL KHAN ET AL J. BIOL. CHEM.,1997, vol. 272, p. 8270-8275.

2. It seems that the Applicant validly claims priority. Therefore, D8 is not considered for this preliminary examination as prior art.

3. D1 discloses peptides comprising the sequence DLRL and one peptide containing the all-D-enantiomer DLRL (see peptides SSP and THP of Fig. 1, peptides 1-3, 7-10 of Table 1 and peptides 1-4, 8-11 of Table 2). SSP and type IV collagen inhibit adhesion of carcinoma cells to an extracellular matrix (see Fig. 4 and 5 Panel). For these inhibition experiments, the peptides are adsorbed onto polystyrene plates (= peptide- substrate combination; see Material and Methods, 'Cell Adhesion') after dilution in a sulfoxide/water mixture (= pharmaceutical composition). Therefore, the subject-matter of claims 1, 2, 6-9, 11, 13, 17, 20, 22 and 24 is not novel (Art 33(2) PCT).

   D2 discloses the peptide 15 comprising the sequence SIKV and that slightly inhibits alveolar formation (=inhibits proliferation; compare Area Values in Table II, col. 11). The peptide 17 (Table II, col. 11), which has been proposed as the alpha3beta1 integrin binding site (col. 8, l. 29-33) has been disclaimed from claim 1 of the present application. It has been suggested in D2 that its peptides can be used to inhibit cell attachment (col. 6, l. 25-29) and angiogenesis (col. 6, l. 38). However, the peptides 15 and 17 have not been used in the examples. This renders only the subject-matter of claims 1 and 2 not novel (Art 33(2) PCT).

D3 discloses the peptides p1 (Table 1, p. 11) and p9 (Table 2, p. 12) comprising sequences NLRI. P9 was coupled with the protein KLH (=peptide-substrate combination; = pharmaceutical composition; =peptide conjugate; see p. 53, l. 7). It is suggested that said peptides can inhibit aggregation of platelets (p. 24, l. 31-32). Therefore, the subject-matter of claims 1, 2, 11, 13 and 15 is not novel (Art 33(2) PCT).

The peptide R30 (Table 1, p. 7) of D4 contains one of the sequences disclaimed in claim 1. For anti-peptide ELISA (see p. 9, l. 21), the wells were coated with this peptide. Therefore, the subject-matter of claim 11 does not meet the requirements of Art. 33(2) PCT.

D5 discloses the peptides D-Hep III and L-Hep III (see sequences in Abbreviations, p. 15404), containing the sequence DLRL, inhibit adhesion of said melanoma and breast carcinoma cells (=cells expressing alpha3beta1 integrin) to type IV collagen and fibronectin (=extracellular matrix; see Figs. 4 and 5) and invasion (= inhibition of cell motility; see Fig. 6) of basement membrane. For the 'cell adhesion assays', 'cell spreading assays', 'cell motility assays', 'inhibition of cell adhesion assays' and 'affinity chromatography and immunoprecipitation analysis', the peptides were attached to a substrate (= peptide-substrate combination; see Material and Methods) and for the 'hydrolysis analysis', the peptides were dissolved in water (=pharmaceutical composition; see Material and Methods). Thus, the subject-matter of claims 1, 2, 6-9, 11,13, 20, 22, 24-28 does not fulfil the requirements of Art. 33(2) PCT.

D6 discloses the peptides C28, C28a and C28g-I comprising the sequence DIRV and the peptides C68, C68a and C68g-I comprising the sequence SIKI (see Table II, p. 32202). C68 do not affect tube formation (Table III, p. 32204). The peptides were dissolved in Milli-Q water (=sterile composition; see Material and Methods, 'Preparation of Peptide-conjugated Sepharose Beads') and coupled to polystyrene and sepharose beads (=peptide-substrate combination; =pharmaceutical composition; see Material and Methods, 'Synthetic Peptides and Laminin-1' and 'Preparation of Peptide-conjugated Sepharose Beads'). This renders the subject-matter of claims 1, 2, 11, 13, 14 and 17 not novel (Art. 33(2) PCT).

D7 describes that alpha3beta1 integrin is the major human TSP1-binding integrin on several human breast carcinoma cell lines. TSP1 have diverse effects on cell adhesion, motility, proliferation and survival (see abstract and introduction). Since TSP1 comprises the sequence FQGVLQNVRFVF, the subject-matter of claims 4, 20-22, 24 and 25 is not novel (Art. 33(2) PCT).

D9 discloses peptide SIKVAV, which stimulates uPA expression, in sterile aqueous solutions (=pharmaceutical composition; = sterile composition; see Material and Methods, 'Effect of Synthetic Laminin Peptides on Macrophages uPa and MMP Expression', p. 8271). Therefore, the subject-matter of claims 1, 2, 13 and 14 is not novel (Art. 33(2) PCT).

In summary, the subject-matter of claims 1, 2, 4, 6-9, 11, 13-15, 17, 20-22 and 24-28 is not novel (Art 33(2) PCT).

The subject-matter of the claims 3, 5, 10, 12, 16, 18, 19, 23, 29-45 is novel over the content of D1-D9.

4. Taking D7 as the closest prior art, the problem to be solved can be regarded as the provision of alternative compounds (peptides) that modulate the binding of alpha3beta1 integrins with their ligands.

The solution proposed in the application consists in the peptides comprising the sequences R1-X1-X2-X3-X4-R2.

It is known from D7 that alpha3beta1 integrin is the major human TSP1-binding integrin on several human breast carcinoma cell lines (see D7, Abstract). Other sequences that bind to alpha3beta1 integrin are also known, like L-Hep-III and D-Hep-III (see D5, abstract) and the GD-6 peptide (see application, p. 10, l. 21). In the knowledge of these sequences, the skilled person would be able to search for homologue sequences with the known sequence of TSP1 without the exercise of an inventive activity. Reverse peptides have been shown to be active (see D5). On the other hand, it is widely known in the field that processes like adhesion, motility and proliferation are related and can be use in treatment of diseases like cancer. Therefore, the subject-matter of claim 1-45 is not inventive.

The peptides C28 and C68 of D6, which fall within the scope of claims 1, 2, 11-45 mediate cell attachment through alpha2beta1 integrin or non-integrin receptors as stated on p. 32203, L.H. col, 1st paragraph of D6. Since all the compounds falling within the scope of said claims do not solve the technical problem, ie modulate the binding of alpha3beta1 integrins with their ligands, the subject-matter of claims 1, 2, 11-45 does not meet the requirements of Art 33(3) PCT.

It is also doubtful that any peptide comprising the sequences claimed would solve the problem stated above since said sequences could be sterically hindered or not exposed in the peptide, hindering the binding to alpha3beta1 integrins. Therefore, the subject-matter of claim 1-45 is not inventive (Art. 33(3) PCT).

Re Item VII

Certain defects in the international application

1. In Table 2, the meaning of the symbol + of the IC50 value of peptide 689 is not known.

2. The "solid bars" mentioned in the "Brief Description of the Drawings" of several figures cannot be found in the corresponding figures.

3. In Figure 19A, the peptide concentration appears to range from 1-100 uM and not 1-40 uM as mentioned in the "Description of the Drawings".

4. The vague and imprecise statement in the description "and the like" on p. 12, l. 11, p. 17, l. 32, p. 24, l. 1 and p. 50, l. 7 and "without limitation" on p. 22, l. 12 and 15 and p. 24, l. 9 imply that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity of the claims (Article 6 PCT) when used to interpret them (see the PCT Guidelines, C-III, 4.3a).

5. The term "about" used in claims 2 and 9 and on page 28, l. 21 and p. 50, l. 8 of the description, referred to numerical quantities renders unclear the scope of said claim (Art. 6 PCT).

6. Expressions as "incorporated by reference" (p. 50, l. 4-5) are not allowable (see Guidelines PCT II-4.17) since the patent specifications should, regarding the essential features of the invention, be self-contained, that is, capable of being understood without reference to any other document.

7. In claim 8, X2, X3, X4 are missing the '-symbol in order to be in agreement with the retro-inverso synthetic peptide disclosed.

8. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D6 and D9 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII
Certain observations on the international application

1. Claim 4, which is dependent from claim 1, includes subject-matter explicitly disclaimed from claim 1, ie peptides comprising the sequence FQGVLQNVRFVF.

2. The claims 31, 37 and 44 do not fulfil the requirements of Art. 6 PCT, since the expressions "under condition supportive of cell division" (claim 31), "effective amount" (claim 37) and "composition sufficient to inhibit" (claim 44), have not a well-defined meaning and the skilled person does not know which are the conditions and amounts to which those expressions make reference.

3. The method of claim 26 does not meet the requirement of Art. 5 PCT since the skilled person does not know what kind of cell should be selected in order to carry out the method without undue experimentation effort. Moreover, it seems from Figs. 11-14, that inhibition of cell motility is a density- and substrate- dependent method, features which seem to be essential to carry out the method. Therefore, claim 26 does not meet the requirements of Art. 6 PCT.

4. The subject-matter of claim 6 does not meet the requirements of Art. 6 PCT since it is not known whether a "partial or full retro-inverso peptide sequence" means simply a peptide containing D-amino acids (which seems to be the case) or other kind of peptides.

5. It is understood that the peptides of claim 1 are defined by the amino acid replacements stated in said claim for the groups R1, X1, X2, X3, X4. However, the extensive definition of a peptide given on pages 12-13, when used to interpret said claim, renders its subject-matter unclear (Art. 6 PCT) since it is not known which are the specific embodiments considered as equivalents, analogs or mimetics and which not. The same objection can be raised for claim 8 in combination with the definition of a retro-inverso peptide on pages 13-14.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organizati n
International Bureau

(43) International Publication Date
25 January 2001 (25.01.2001)

PCT

(10) International Publication Number
WO 01/05812 A3

(51) International Patent Classification[7]: C07K 14/78, A61K 38/39, A61P 35/00, A61F 2/06

(21) International Application Number: PCT/US00/18986

(22) International Filing Date: 12 July 2000 (12.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/144,549 15 July 1999 (15.07.1999) US

(71) Applicant *(for all designated States except US)*: **THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES** [US/US]; Bethesda, MD 20892 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ROBERTS, David, D.** [US/US]; 6808 Persimmon Tree Road, Bethesda, MD 20817 (US). **KRUTZSCH, Henry, C.** [US/US]; 9704 Depaul Drive, Bethesda, MD 20817 (US).

(74) Agents: **DOW, Karen, B.** et al.; Townsend and Townsend and Crew LLP, Two Embarcadero Center, 8th Floor, San Francisco, CA 94111-3834 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

(88) Date of publication of the international search report:
3 May 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/05812 A3

(54) Title: PEPTIDES AND THEIR UTILITY IN MODULATION OF BEHAVIOR OF CELLS EXPRESSING α3β1 INTEGRINS

(57) Abstract: The present invention relates to a peptide comprising the sequence R_1-X_1-X_2-X_3-X_4-R_2, wherein X_1 is selected from the group consisting of N, Q, D and S; X_2 is selected from the group consisting of V, I and L; X_3 is selected from the group consisting of R and K; and X_4 is selected from the group consisting of V, I, L and F; R_1 is a hydrogen or a peptide of 1 to 6 amino acids, and acyl or an aryl group; and R_2 is a peptide of 1 to 3 amino acids, a hydroxide or an amide. The invention also relates to partial or full retro-inverso peptides comprising the above sequences. The invention also relates to peptide-substrate combination comprising a substrate suitable for cell growth and the peptide of the invention, and to a vascular graft and an artificial blood vessel comprising the peptide-substrate combination. The invention also relates to a pharmaceutical composition and a peptide conjugate comprising the peptide of the invention. The invention also relates to a method of inhibiting adhesion of a cell expressing α3β1 integrin to an extracellular matrix, inhibiting α3β1-integrin-mediated cell motility, inhibiting α3β1-integrin mediated cell proliferation, promoting α3β1-integrin mediated cell proliferation and inhibiting angiogenesis utilizing the peptides of the invention.

PATENT COOPERATION TREATY

PCT

10/030735

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
15280-397-1PC		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 18986	12/07/2000	15/07/1999
Applicant		
THE GOVERNMENT OF THE U.S.A. AS REPRESENTED BY...		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[X] furnished subsequently to this Authority in written form.

[X] furnished subsequently to this Authority in computer readble form.

[X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to the peptides of claim 1 and/or 8 having the alleged activity i.e. being able to modulate binding of alpha3beta1 integrins with their ligands.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]/US 00/18986

A. CLASSIFICATION OF SUBJECT MAT[redacted]
IPC 7 C07K14/78 A61K38/39 A61P35/00 A61F2/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, EPO-Internal, WPI Data, PAJ, STRAND, CHEM ABS Data, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MILES A J ET AL: "PROMOTION OF CELL ADHESION BY SINGLE-STRANDED AND TRIPLE-HELICAL PEPTIDE MODELS OF BASEMENT MEMBRANE COLLAGEN ALPHA1(IV)531-543. EVIDENCE FOR CONFORMATIONALLY DEPENDENT AND CONFORMATIONALLY INDEPENDENT TYPE IV COLLAGEN CELL ADHESION SITES" JOURNAL OF BIOLOGICAL CHEMISTRY,US,AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 269, no. 49, 1 December 1994 (1994-12-01), pages 30939-30945, XP000615314 ISSN: 0021-9258 page 30941, left-hand column, paragraph 1; figure 1; tables I,II page 30942, right-hand column, paragraph 2 -page 30945, left-hand column, last paragraph -/--	1,2,6,7, 31,32, 37,38, 40-42

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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Date of the actual completion of the international search	Date of mailing of the international search report
17 January 2001	06/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fuhr, C

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C.(Continuation) DOCUMENTS CONSID[redacted]D TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.

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INTERNATIONAL SEARCH REPORT

International Application No
[redacted]/US 00/18986

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